

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
2 August 2001 (02.08.2001)

PCT

(10) International Publication Number
WO 01/55087 A1

(51) International Patent Classification: **C07C 209/00**

(21) International Application Number: PCT/US01/01702

(22) International Filing Date: 18 January 2001 (18.01.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/492,327 27 January 2000 (27.01.2000) US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:

US 09/492,327 (CON)
Filed on 27 January 2000 (27.01.2000)

(71) Applicant (for all designated States except US): **BOULDER SCIENTIFIC COMPANY** [US/US]; 598 Third Street, P.O. Box 548, Mead, CO 80542 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **SULLIVAN, Jeffrey, M.** [US/US]; 3125 Morey Court, Loveland, CO 80537 (US). **RUSO-RODRIGUEZ, Sandra** [US/US]; 3002 Falcon Ridge Cove, Laredo, TX 78045 (US).

(74) Agent: **IRONS, Edward, S.**; 3945 - 52nd Street, N.W., Washington, DC 20016 (US).

(81) Designated States (national): AU, CA, JP, NZ, US.

(84) Designated States (regional): European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).

Published:

— with international search report
— with amended claims and statement

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SYNTHESIS OF N⁴, N^{4'}-DIPHENYL-N⁴, N^{4'}-DI-M-TOLYL-BIPHENYL-4,4'-DIAMINE FROM AN UNSYMMETRICAL AMINE

(57) Abstract: Novel (4-halophenyl) biphenyl tolyl amines are described.

WO 01/55087 A1

SYNTHESIS OF N⁴,N⁴'-DIPHENYL-N⁴,N⁴'-DI-M-TOLYL-BIPHENYL-4,4'-DIAMINE FROM AN UNSYMMETRICAL AMINE

This application is a continuation of United States application Serial No. 09/492,327 filed 27 January 2000.

FIELD OF THE INVENTION

This invention relates to the nickel catalyzed formation of novel unsymmetrical tertiary amines. More particularly, the invention relates to

(4-halo-phenyl)-phenyl-*m*-tolyl-amines (I) which may be converted to

N⁴,N⁴'-diphenyl-N⁴,N⁴'-di-*m*-tolyl-biphenyl-4,4'-diamine (II) by nickel catalyzed coupling.

BACKGROUND OF THE INVENTION

It is known to produce (II) by palladium catalyzed amination using *m*-methyldiphenylamine, 4,4'-dibromobiphenyl and tri-tert-butyl phosphine. See Yamamoto, T., et al., Tetrahedron Letters (1998) 39:2367-2370. It is also known to produce (II) by reaction of *m*-methyldiphenyl amine with 4,4'-diiodobiphenyl under copper powder in potassium hydroxide or other bases in high boiling solvents at 150-200°C. See, e.g., United States patent 4,764,625. 1,10-phenanthroline has been used to ligate copper and the use of Cu(I) salts has been reported to reduce the temperature of this reaction to 125°C. See Goodbrand, J.Org.Chem. (1999) 64:4290 and United States patents

-2-

5,654,482; 5,648,539; 5,648,542; 5,705,697; 5,723,669 and 5,723,671. Coupling of chlorobenzene to afford biphenyl and 4-chloroaniline to afford 4,4'-diaminobiphenyl using NiCl_2 , triphenylphosphine, zinc and DMF with and without 2,2' bipyridyl is described in J.Org.Chem. (1986) 51:2367-2370. Patent 4,263,466 describes a method for coupling aryl chlorides in which a nickel catalyst is generated in situ from nickel salts and excess reducing agents.

In general, a problem exists in that prior art procedures for producing (II) and similar compounds entail the use of biphenyl starting material including expensive dihalobiphenyls and harsh high temperature conditions.

A need exists for a more cost effective method for producing such compounds.

There is a particular need for a mild, low temperature nickel catalyzed synthesis of an intermediate which may be converted to compounds typified by (II).

SUMMARY OF THE INVENTION

Pursuant to this invention, the biphenyl moiety of compounds such as (II) is assembled after the amine moieties are in place. A novel intermediate (I) is synthesized. The intermediate is then coupled in a mild nickel catalyzed reaction. A novel intermediate, e.g., unsymmetrical, triarylamine (4-halo-

-3-

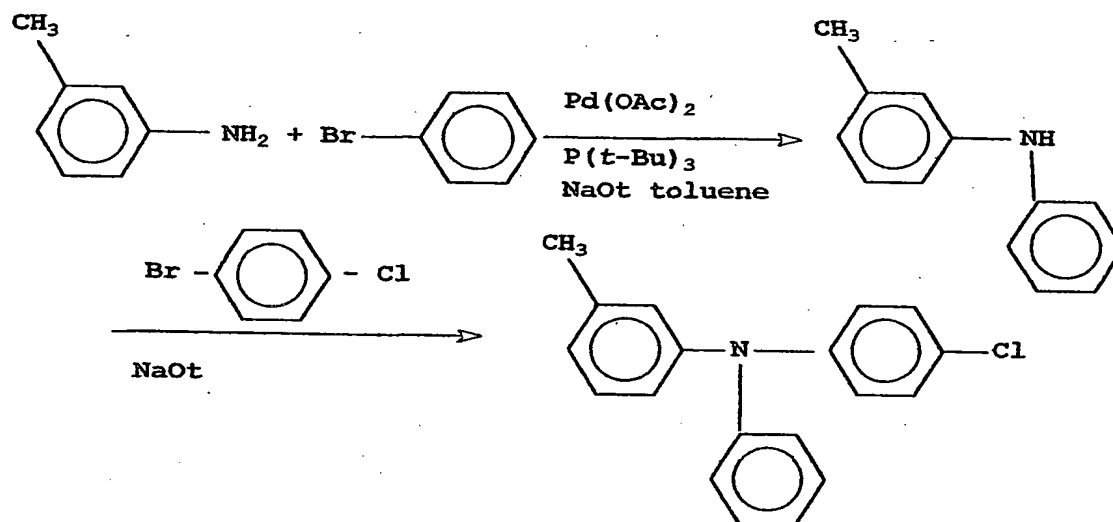
phenyl)phenyl-*m*-tolyl amine (I) is first synthesized from cheap building blocks, typically *m*-toluidine, bromobenzene, and 1,4 bromo-chlorobenzene to yield triaryl amine chloride (I). The synthesis is accomplished via two, sequential palladium catalyzed aminations in one pot. The compound (I) may be crystallized in good yield, e.g., above 80% yield, and high purity, e.g., 95% purity. (II) is produced by nickel catalyzed coupling of (I).

DETAILED DESCRIPTION OF THE INVENTION

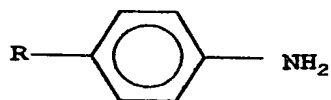
Synthesis of (I) (4-Chloro-Phenyl-*M*-Tolyl Amines)

In the first step, the pot is charged under nitrogen with palladium acetate, tri-*tert*-butyl phosphine and dry deoxygenated toluene. A first reaction mixture of a red color results. Bromobenzene, sodium *t*-butoxide and *m*-toluidine are added sequentially under nitrogen. The reaction is heated with stirring under reflux for a time sufficient, e.g., 1 to 2.5 hours, to produce a reaction mixture containing 95-97% of *m*-methyl diphenyl amine. 1,4-bromo chlorobenzene and sodium *t*-butoxide are then added, and the reaction is stirred to reflect overnight to afford (I). The reaction is illustrated by Equation 1:

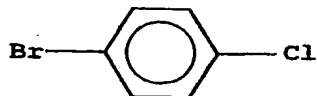
-4-

Equation 1

In Equation 1, *m*-toluidine may be replaced by an compound of the formula:

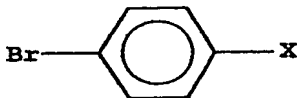


in which R is an ortho, meta, or para C_1 to C_{10} alkyl substituent,



-5-

may be replaced by any compound of the formula:



in which X is any halogen or triflate.

EXAMPLE 1

Preparation of (4-chloro-phenyl)-phenyl-*m*-tolyl amine(I)

Under nitrogen, a flask is charged with 138 mg (0.0006 mol) of palladium acetate, 0.48 g (0.002 mol) of tri-tert-butylphosphine, 180 grams of dry, deoxygenated toluene. The solution is stirred for 5 minutes until the pale yellow color changed to a red color. The other reagents are added sequentially under nitrogen: 22 mL (0.2 mol) of bromobenzene, 25.3 g (0.26 mol) of sodium *t*-butoxide and *m*-toluidine (22 mL, 0.2 mol). The reaction is heated with stirring to reflux for 2.5 hours, at the end of which it was cooled down and analyzed by GC/MS to contain 95-97% of *m*-methyldiphenylamine. 25.8 g (0.26 mol) of sodium *t*-butoxide and 38.8 g (0.2 mol) of 1,4-bromochlorobenzene are added; the reaction is filled with nitrogen, and heated to reflux with stirring for 18 hours. The reaction is cooled, water is added, extract the aqueous with toluene. The combined organic layers are dried

-6-

over sodium sulfate, filtered through a pad of neutral alumina, and the filtrate is distilled to remove the bulk of the solvent. The concentrated solution is treated with MeOH slowly with stirring. The solid is collected to afford 50 g (83%) of (4-chloro-phenyl)-phenyl-*m*-tolyl amine as an off-white solid.

Synthesis of (II)

Coupling of (I) to produce (II) may be accomplished in two steps, preferably in one pot.

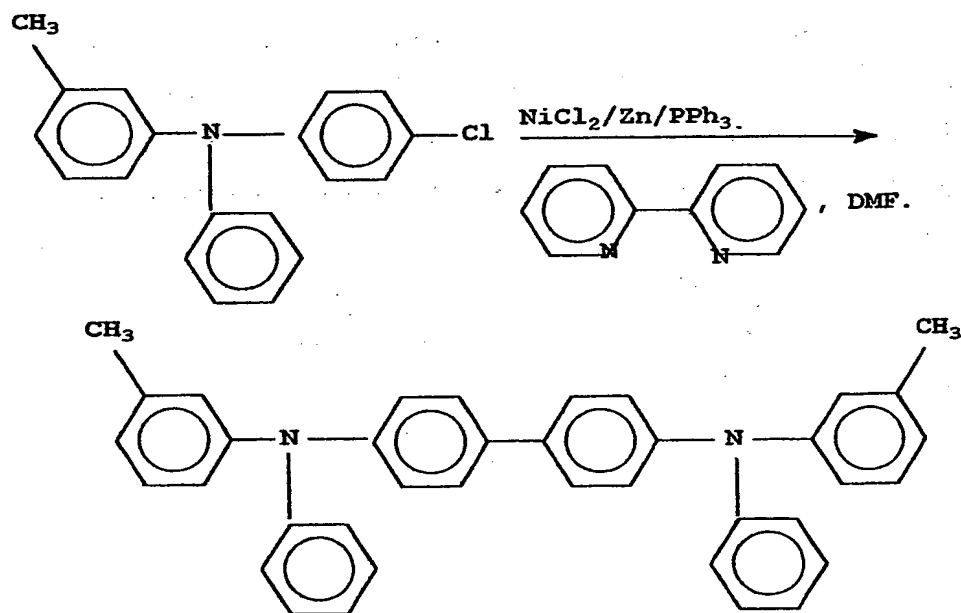
In a first step, a dry nitrogen filled pot is charged with zinc powder, triphenyl phosphine 2,2' bipyridyl, anhydrous NiCl₂ deoxygenated DMF and activated molecular sieves. Presently preferred coupling conditions are 0.5 eq NiCl₂, 0.05 eq 2,2' pyridyl, 0.26 eq triphenylphosphine, 1.5 eq zinc in 60-70°C DMF. The mixture is heated under conditions effective to produce a color change from gray to dark brown. Appropriate conditions include heating at a temperature of 50°C to 100°C, preferably about 65°C, for about 10-15 minutes.

Thereafter, in a second step, the pot temperature is maintained at about 50-60°C, a solution of (4-chloro-phenyl)-phenyl-*m*-tolyl amine (I) in DMF is added dropwise. The reaction mixture is maintained at about 60-65°C with stirring, preferably until complete consumption of (I) as may be evidenced by TLC analysis is achieved. The reaction mixture may then be diluted

-7-

with an inert diluent, such as dichloromethane, diethyl ether, or toluene, and filtered to remove excess zinc and solids. The filtrate is washed with water several times resulting in the formation of an aqueous layer and a dichloromethane layer which is separated, treated with silica gel, filtered, and the filtrate is treated with neutral alumina. The product (I) is recovered by crystallization.

The reaction is illustrated by Equation 2:



Equation 2

-8-

In Equation 2, the reactant (a) may be replaced by a similar compound in which $-CH_3$ is replaced by any ortho, meta, or para C_1 to C_{10} alkyl group, and Cl is replaced by bromine or fluorine.

EXAMPLE 2

Preparation of $N^4, N^{4'}$ -Diphenyl- $N^4, N^{4'}$ -di-*m*-tolyl-biphenyl-4,4'-diamine:

Charge a dry, nitrogen filled flask with 4.9 g (0.07 mol of zinc powder), 3.4 g (0.01 mol) of triphenylphosphine. 0.4 g (0.002 mol) of 2,2'-bipyridyl, 0.3 g (0.002 mol) of anhydrous $NiCl_2$, 30 mL of dry, deoxygenated DMF, and 2 g of activated 3A molecular sieves. The mixture is heated under nitrogen to 65°C until the gray color changed to dark brown (about 10-15 minutes). Maintaining a pot temperature of 60°C, a solution of (4-chloro-phenyl)-phenyl-*m*-tolyl amine (13.4 g, 0.04 mol) in 40 mL of DMF is added dropwise. After addition is over, the reaction is stirred between 60-65°C for 2-5 hours, until TLC analysis revealed complete consumption of starting aryl chloride. The reaction is diluted with dichloromethane, filtered to remove excess zinc and solids. The filtrate washed four times with water. The dichloromethane layer is dried over sodium sulfate, filtered and concentrated to a reduced volume. The dichloromethane solution is treated with silica gel,

-9-

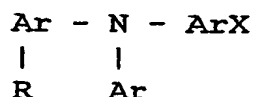
filtered, and solution is treated with neutral alumina until the solution is pale yellow. The product is crystallized twice to afford 8.7 g (80%) of N⁴,N^{4'}-diphenyl-N⁴,N^{4'}-di-*m*-tolyl-biphenyl-4,4'-diamine as a white solid. An analytical sample can be obtained by chromatography using a slow gradient of 0-5% ethyl acetate in hexane.

5

-10-

WE CLAIM:

1. (4-chloro-phenyl)-phenyl-*m*-tolyl-amine.
2. A compound having the graphic formula:



in which Ar is any aryl group, wherein each Ar may be the same as or different from any other Ar; R is an ortho, meta or para-alkyl group; and X is a halogen.

3. The claim 2 compound in which each Ar is phenyl.
4. The claim 2 or claim 3 compound in which R is a C₁ to C₁₀ alkyl group.
5. The claim 2 or claim 3 compound in which X is chlorine.
6. A method for synthesizing (4-chloro-phenyl)-phenyl-*m*-tolyl-amine (I) which comprises:
 - (i) charging a nitrogen filled reactor with palladium acetate, tri-tert butyl phosphine and deoxygenated toluene;
 - (ii) agitating the step (i) pale yellow reaction mixture to produce a red color and thereafter
 - (iii) sequentially adding to the step (ii) red reaction mixture bromobenzene, sodium *t*-butoxide, and *m*-toluidine;

-11-

- (iv) heating the step (iii) reaction mixture to produce a step (iv) reaction mixture containing *m*-methylphenyl amine;
- (v) treating said step (iv) reaction mixture with sodium *t*-butoxide and 1,4-chlorobromobenzene, wherein a step (v) reaction mixture containing (I) is produced.

7. The method of claim 6 further comprising a step

- (vi) recovering (I) as a solid from said step (v) reaction mixture.

8. The method of claim 6 further comprising a step

- (vii) converting said solid (I) recovered in step (vi) to (II).

9. The method of claim 8 wherein said converting step (vii) is accomplished by a nickel catalyzed coupling of (I).

10. A method of coupling (I) to produce (II) which comprises:

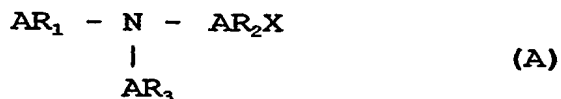
- (i) charging a reactor with zinc powder, triphenylphosphine, 2,2'-bipyridyl, NiCl_2 and DMF, wherein a mixture of a gray color is produced;

-12-

- (ii) heating said step (i) mixture of gray color in said step (i) reactor to produce a step (ii) mixture of dark brown color;
- (iii) adding a solution of (I) in DMF to said step (ii) mixture to produce a step (iii) reaction mixture in said step (i) reactor; and
- (iv) heating said step (iii) reaction mixture, wherein a step (iv) reaction mixture containing (II) is produced.

11. The claim 10 method further comprising a step (v) recovering said (II) from said step (iii) reaction mixture.

12. A method of coupling a triaryl amine having the formula (A):

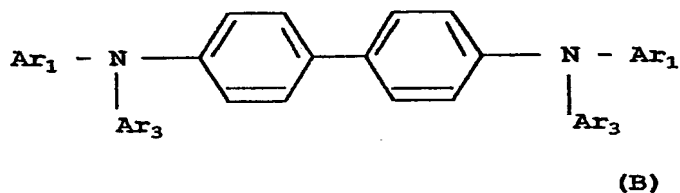


wherein AR_1 , AR_2 and AR_3 are the same or different aryl groups, and X is a halogen wherein at least one of said aryl groups may or may not have one or more ortho, meta or para C_1 to C_{10} alkyl substituent which comprises:

- (i) charging a nitrogen filled reactor with a mixture of zinc powder, triphenylphosphines, 2,2'-bipyridyl, anhydrous NiCl_2 and deoxygenated DMF, wherein said mixture is gray in color;

-13-

- (ii) heating said step (i) mixture in said reactor to provide a step (ii) mixture dark brown in color;
- (iii) treating said step (ii) mixture in said reactor with a DMF solution of a compound of formula (A), wherein step (iii) reaction mixture containing a compound of formula (B)



is produced.

AMENDED CLAIMS

[received by the International Bureau on 28 June 2001 (28.06.01)]

Original claims 2-5 cancelled; new claims 13-15 added;
remaining claims unchanged (3 pages)]

1. (4-chloro-phenyl)-phenyl-*m*-tolyl-amine.

2. [CANCELLED]

3. [CANCELLED]

4. [CANCELLED]

5. [CANCELLED]

6. A method for synthesizing (4-chloro-phenyl)-
phenyl-*m*-tolyl-amine (I) which comprises:

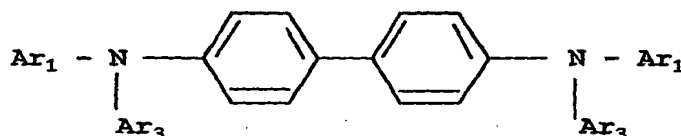
(i) charging a nitrogen filled reactor with
palladium acetate, tri-tert butyl
phosphine and deoxygenated toluene;

(ii) agitating the step (i) pale yellow
reaction mixture to produce a red color
and thereafter

(iii) sequentially adding to the step (ii) red
reaction mixture bromobenzene, sodium *t*-
butoxide, and *m*-toluidine;

(iv) heating the step (iii) reaction mixture to
produce a step (iv) reaction mixture
containing *m*-methylphenyl amine;

(v) treating said step (iv) reaction mixture
with sodium *t*-butoxide and 1,4-
chlorobromobenzene, wherein a step (v)
reaction mixture containing (I) is
produced.

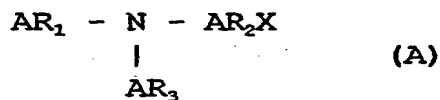


(B)

is produced.

13. A method which comprises:

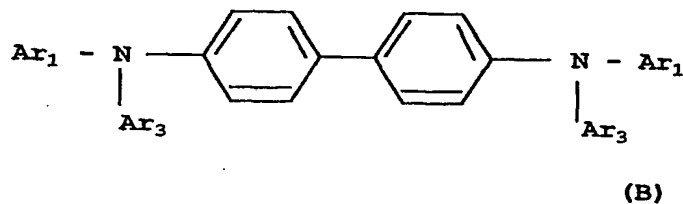
(i) providing a reactor containing monomeric triaryl amine molecules having the formula (A):



wherein AR_1 , AR_2 and AR_3 are the same or different aryl groups, and X is a halogen wherein at least one of said aryl groups may or may not have one or more ortho, meta or para C_1 to C_{10} alkyl substituent; and

(ii) subjecting said monomeric triaryl amine having the formula (A) as contained in said step (i) reactor to conditions effective to cause coupling of two of said monomeric triaryl amine molecules in said reactor,

wherein a reaction mixture containing a compound
of formula (B)



is produced in said step (i) reactor.

14. The method of claim 13, wherein said
monomeric triaryl amine contained in said step (i)
reactor is (4-chloro-phenyl)-phenyl-*m*-tolyl amine.

15. The method of claim 13, wherein said
conditions effective to cause coupling comprise nickel
catalysis.

STATEMENT UNDER ARTICLE 19

International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Gentlemen:

The attached amendments to the claims should have no impact
on the description and the drawings.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/01702

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07C 209/00

US CL : 564/405, 433, 432, 434

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 564/405, 433, 432, 434Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONEElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chemical Abstracts Online, Accession No. 120:284968, ONO et al. Electrophotographic photoreceptor containing azo compound and triphenylamine derivative. 07 December 1993, JP 05323642, see compound m=154924-90-0 and entire abstract.	1-5

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

22 May 2001 (22.05.2001)

Date of mailing of the international search report

05 JUN 2001

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks
Box PCT

Washington, D.C. 20231

Facsimile No. (703)305-3230

Authorized officer

SAMUEL BARTS

Telephone No. (703)305-3230

TERRY J. DEY

PARALLEL SPECIALIST

TECHNOLOGY CENTER 100

